Test Definition: GNTHR

Thrombosis Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating hereditary thrombosis in patients with a personal or family history suggestive of a hereditary thrombosis disorder

Confirming a hereditary thrombosis disorder diagnosis with the identification of a known or suspected pathogenic alteration in one or more of 16 genes associated with a variety of hereditary thrombosis disorders

Determining the disease-causing alterations within one or more of these 16 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a thrombosis disorder

Identifying the causative alteration for genetic counseling purposes

Prognosis and risk assessment based on genotype-phenotype correlations

Carrier testing for close family members of an individual with a hereditary thrombosis disorder diagnosis

This test is **not intended for** prenatal diagnosis.

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 16 genes associated with a variety of hereditary thrombosis disorders: *ADAMTS13*, *F2*, *F5*, *FGA*, *FGB*, *FGG*, *HRG*, *PIGA*, *PLAT*, *PLG*, *PROC*, *PROCR*, *PROS1*, *SERPINC1*, *SERPIND1*, and *THBD*. See Targeted Genes and Methodology Details for Thrombosis Disorders, Comprehensive Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for a variety of hereditary thrombosis disorders.

Testing Algorithm

A systematic diagnosis through conventional coagulation testing is recommended prior to considering genetic testing for any suspected thrombosis disorder.

Genetic testing for a hereditary thrombosis disorder is indicated if:
-Coagulation tests indicate a deficiency or functional abnormality (note: these tests are best performed in medically stable patients who are not receiving particular anticoagulants)
-There is a clinical suspicion for a hereditary thrombosis disorder due to family history or atypical clinical presentation
-Acquired causes of deficiencies associated with thrombosis have been excluded (eg, vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

However, no screening test exists for detecting defects in a subset of genes on this panel, such as *PROCR* and *THBD*. If

the thrombotic tendency is a concern, a set of clinical guidelines from the British Society for Haematology on testing for heritable thrombophilia is freely available.(1)

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Rare Coagulation Disorder Patient Information
- Targeted Genes and Methodology Details for Thrombosis Disorders, Comprehensive Gene Panel

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Special coagulation testing for evaluating patients with thrombosis or hypercoagulability states should be performed prior to genetic testing. For more information see AATHR / Thrombophilia Profile, Plasma and Whole Blood.

This test is designed to evaluate a variety of thrombophilia.

This test is not designed to evaluate for a single common hereditary thrombosis disorder, such as when an individual has a known family history of antithrombin deficiency, protein C deficiency, or protein S deficiency, specifically. If testing for a particular common hereditary thrombosis disorder is desired, single gene tests are available for the *SERPINC1*, *PROC*, and *PROS1* genes. See GNANT / Antithrombin Deficiency, *SERPINC1* Gene, Next-Generation Sequencing, Varies; GNPRC / Protein C Deficiency, *PROC* Gene, Next-Generation Sequencing, Varies; or GNPRS / Protein S Deficiency, *PROS1* Gene, Next-Generation Sequencing, Varies.

This test is not designed to evaluate hereditary bleeding disorders. If bleeding is the indication for testing and testing for hereditary bleeding disorders is desired, bleeding panels are available. See GNBLF / Bleeding Disorders, Focused Gene Panel, Next-Generation Sequencing, Varies or GNBLC / Bleeding Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Necessary Information

Rare Coagulation Disorder Patient Information **is required.** Testing may proceed without the patient information, however, the information aids in providing a more thorough interpretation. Ordering healthcare professionals are strongly encouraged to fill out the form and send with the specimen.

Specimen Required

Specimen Type: Whole blood

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a bone marrow transplant, call 800-533-1710.

Container/Tube:

Preferred: Lavender top (EDTA)

Acceptable: Yellow top (ACD)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days

Additional Information: To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

Forms

1. Rare Coagulation Disorder Patient Information **(T824) is required**.
2. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

3. If not ordering electronically, complete, print, and send an Coagulation Test Request (T753) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an

underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth).

Determination of a hereditary thrombosis disorder contributing to thrombotic events in an individual or family can be useful for prognosis and risk assessment. Identification of an alteration that is known or suspected to cause disease can also be useful for determining the risk for thrombosis for family members.

This panel evaluates 16 genes associated with a variety of hereditary thrombosis disorders, including thrombotic thrombocytopenic purpura; thrombophilia due to thrombin defect; thrombophilia due to activated protein C resistance; fibrinogen deficiencies (afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia); histidine-rich glycoprotein deficiency; paroxysmal nocturnal hemoglobinuria (somatic); familial hyperfibrinolysis; plasminogen deficiency and dysplasminogenemia; protein C deficiency; purpura fulminans; protein S deficiency; antithrombin deficiency; heparin cofactor 2 deficiency; and thrombomodulin deficiency.

The risk for developing thrombosis associated with these syndromes varies. For example, the relative risk (95% CI) for the incidence of a first-lifetime venous thromboembolism event associated with antithrombin deficiency is 17.5 (9.1-33.8), protein C deficiency is 11.3 (5.7-22.3), and protein S deficiency is 32.4 (16.7-62.9).(2) Several of the genes on this panel have established thrombosis risk or expert group guidelines.(1-6)

Indications for testing include, but are not limited to:
-Individuals with venous thromboembolism (VTE) under the age of 50, recurrent and/or spontaneous VTE, or VTE at an unusual site (eg, hepatic, mesenteric, portal, cerebral veins)
-Individuals with a strong family history of thrombosis or pulmonary embolism
-Individuals with warfarin-induced skin necrosis or neonatal purpura fulminans
-Individuals whose personal or family history indicates coinheritance of multiple hereditary thrombosis

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the

Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic mutations and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible

that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(7) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M. Thrombophilia testing: A British Society for Haematology guideline. Brit J Haematol. 2022 Aug;198(3):443-458
2. Pruthi RK. Optimal utilization of thrombophilia testing. Int J Lab Hematol. 2017;39(s1):104-110
3. Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematol-Am Soc Hematol Educ Program. 2016;1:1-9
4. Tregouet DA, Morange PE. What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. Br J Haematol. 2018;180(3):335-345
5. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 26, 2024. Accessed March 2 , 2026. Available at: www.isth.org/page/GinTh_GeneLists
6. Megy K, Downes K, Simeoni I, et al. Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019;17(8):1253-1260
7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion-insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for

the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Thrombosis Disorders, Comprehensive Gene Panel and Methodology Details for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ADAMTS13*, *F2*, *F5*, *FGA*, *FGB*, *FGG*, *HRG*, *PIGA*, *PLAT*, *PLG*, *PROC*, *PROCR*, *PROS1*, *SERPINC1*, *SERPIND1*, and *THBD*

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81443

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNTHR	Thrombosis Comprehensive Panel, NGS	105336-2

Result ID	Test Result Name	Result LOINC® Value
619272	Test Description	62364-5
619273	Specimen	31208-2
619274	Source	31208-2
619275	Result Summary	50397-9
619276	Result	82939-0
619277	Interpretation	59465-5
619278	Additional Results	82939-0
619279	Resources	99622-3
619280	Additional Information	48767-8
619281	Method	85069-3
619282	Genes Analyzed	82939-0
619283	Disclaimer	62364-5
619284	Released By	18771-6